REMARKS

I. STATUS OF CLAIMS

Claims 45-59, 61, 62, and 64-75 are pending. Claims 45 and 64 are amended herein. Claims 39-44, 60, 63, and 76 are cancelled without prejudice or disclaimer. Written description support for the amendments can be found in the specification and the claims. Thus, no new matter is added by the amendments provided herein. Entry of the amendments is respectfully requested.

II. REJECTIONS UNDER 35 U.S.C. § 103

A. Rejection over Griffiths

Claims 45-59 and 63-67 are rejected under 35 U.S.C. § 103(a) over BRYAN GRIFFITHS & DENIS LOOBY, *Scale-Up of Suspension and Anchorage-Dependent Animal Cells, in* 75 METHODS IN MOLECULAR BIOLOGY: BASIC CELL CULTURE PROTOCOLS 59, 59-75 (Jeffrey W. Pollard & John M. Walker eds., 2d ed. 1997) ("Griffiths"). Final Office Action at pp. 2-12. Applicant disagrees and traverses the rejection for at least the following reasons.

To establish a *prima facie* case of obviousness, the Examiner has the burden of establishing that the prior art references teach or suggest all the claim limitations. *See In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Claim 60 is not rejected as obvious over Griffiths. Independent claim 45 has been amended to include the recitations of claim 60. Thus, for at least this reason claim 45, as amended, is not obvious over Griffiths.

In addition, Applicant submits that the Examiner misunderstands the claimed element that "the passage number of each production batch is between master cell

bank and extended cell bank." According to the Examiner, "MCB and ECB are properly considered time limits, or range limits, on the passage number of the cells, and wherein the characteristic defining the ECB is the ability to produce biological product, any cell which is still capable of producing the biological product will be considered to be within the MCB-ECB range." Final Office Action at p. 5. Applicant respectfully disagrees.

Contrary to the Examiner's assertion, the claim element "the passage number of each production batch is between master cell bank and extended cell bank" does not merely define a time period. In classical serial production, as described in Griffiths, the number of doubling of cells derived from the manufacturers working cell bank at the moment of harvest is known up front within certain limits. *See* Applicant's specification at p. 4, lines 15-16. A maximum allowable generation number is set to the production system at the onset. *Id*. at lines 16-17. In contrast, in the claimed method, a bioreactor (manufacturer's working cell bank) is fed with cells from the master cell bank. The cells from the working cell bank are propagated to a specific and characterized passage number for an extended cell bank. *See id*. at lines 19-20. Once the extended cell bank is fully characterized it allows one to produce the biological product with cells at any passage number between master cell bank and extended cell bank since it may be assumed that the cells have not changed. *See id.* at lines 29-32. As a result, tests on the manufacturer's working cell bank can be limited to sterility testing, which is a particular advantage of the claimed invention. *See id*. at lines 32-33.

Further, the Examiner concludes that "[o]nce cells are no longer capable of producing the biological product, the cells are considered to have surpassed the ECB." Final Office Action at p. 5. This, however, is not the criterion for defining the extended

cell bank according to the specification. First, as discussed above, Griffiths does not teach or suggest that "the passage number of each production batch is between master cell bank and extended cell bank" or that "the extended cell bank is validated and fully characterized with respect to growth characteristics, freedom of adventitious, extraneous and endogenous agents at the different stages, karyology, and iso-enzyme analysis." In addition, the meaning of these claim limitations is to guarantee for regulatory purposes that the cells have not changed in their specifications. As the specification indicates "the maximum number of cell passages can be defined by ECB. Production passage number . . . , hence, is irrelevant within the limits set by ECB. As a consequence, such maximum number of passages is to be obeyed in view of regulatory restrictions." Applicant's specification at p. 4, lines 19-23. Thus, it appears that the Examiner does not appreciate the meaning or purpose of the master cell bank and extended cell bank as used herein. Indeed, in the May 27, 2011, Office Action, the Examiner asserts that "as long as cells are capable of producing the desired biological product, they are considered between MCB and ECB" and "when the cells have reached a point of senescence at which the cell culture can no longer be employed." Office Action dated May 27, 2011, at p. 6. This is neither the definition nor the purpose of the passage numbers (MCB -ECB).

Finally, without Applicant's invention, the production of biologicals such as viruses for vaccines requires the growth of a vast array of cells all having the same passage number. *See, e.g., Wiktor et al.,* U.S. Pat. No. 4,664,912, at col. 2, lines 58-68; *see also* Applicant's specification at p. 1, lines 15-20; and at p. 4, lines 26-34. In Wiktor's method, vessel upon vessel of cells all having the same passage number were

prepared, and then seeded with virus for the production of vaccine. That created an enormous logistical problem of managing preproduction batches and harvesting the virus at the optimum time. Key to that method was the production number of the cells: the production number had to be the same for every production batch. As Applicant explains: "In classical serial production lines the number of doubling of the cells derived from the MWCS at the moment of harvest is known up front within certain limits. A maximum allowable generation number is set to the production system at the onset." Applicant's specification at p. 4, lines 15-17.

Now, Applicant discloses methods that do not require strict adherence to production number. Indeed, "Production passage number (the number of cell passages used prior to production of the biological product), hence, is irrelevant within the limits set by ECB." Applicant's specification at p. 4, lines 20-21. Production number according to the present invention is "irrelevant" in the sense that the same production number is no longer required in all production batches. As Applicant explains, "Once such ECB is fully characterised one may allow to produce the product with cells at any passage number between MCB and ECB[.]" *Id.,* lines 29-31. Therefore, a *different* passage number can be used in production batches, and in some embodiments, the logistical problems mentioned above can be lessened.

For at least the foregoing reasons, the Examiner failed to establish a *prima facie* case of obviousness over Griffiths. Thus, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

B. Rejection over Wiktor alone or in combination with Griffiths and Shimizu

Claims 45-76 are rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 4,664,912 to Wiktor et al. ("Wiktor"). Final Office Action at pp. 12-16. In addition, claims 45-76 are rejected under 35 U.S.C. § 103(a) over Wiktor in view of Griffiths, and further in view of Shimizu et al., "Improved Performance with Multiple Fermentors for Repeated Batch Cultivation for Non-Growth-Associated Products, Biotechnology & Bioengineering, Vol. 27, pp. 743-755 (1985) ("Shimizu"). *Id.* at pp. 16-24. Applicant respectfully disagrees and traverses each of the rejections for at least the following reasons.

As discussed above, the Examiner must show that the prior art references teach or suggest all the claim limitations. *See In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Here, the Examiner has not met this burden because Wiktor, Griffiths, and Shimizu fail to teach or suggest all the elements of independent claims 45 and 64, or the claims that depend therefrom.

Specifically, Wiktor and Griffiths fail to teach or suggest parking the cells at a certain passage number by exposure to an ambient temperature ranging from 17 to 32 degrees C. Indeed, the Examiner admits that Griffiths and Wiktor are deficient in this respect--not rejecting claim 60 over Griffiths, and admitting that Wiktor fails to teach "'parking' the cells after a desired cell volume of the preproduction batch has been reached." *See* Final Office Action at p. 2 and 22. Moreover, one of ordinary skill in the art would not be motivated to park the cells in Wiktor at an ambient temperature. In fact, to do so would be contrary to the teachings of Wiktor, which is directed to growing

the cells as quickly as possible to maximize production of virus. Indeed, the Examiner acknowledges that this is the object of Wiktor's method. *See* Final Office Action at p. 23.

In addition, Wiktor and Griffiths fail to teach or suggest that "the extended cell bank is validated and fully characterized with respect to growth characteristics, freedom of adventitious, extraneous and endogenous agents at the different stages, karyology, and iso-enzyme," the elements recited in claims 63 and 76, and now incorporated in claims 45 and 64. The Examiner asserts that "one having ordinary skill in the art would readily recognize when the cells have reached a point of senescence at which the cell culture can no longer be employed. This is considered to meet the limitation of claims 63 and 76 in that the ECB would have been 'fully characterized' by the person having ordinary skill in the art to determine when the cell line has exhausted its utility." Final Office Action at p. 21. Applicant respectfully disagrees.

The recitations of claims 63 and 76, which are now incorporated into claims 45, and 64, respectively, describe validation and characterization of the extended cell bank, which guarantees that all passage numbers can safely be used for production without any further analytical efforts. This has nothing to do with determining when a cell line has exhausted its utility.

As discussed in Section II.A above, in Wiktor's method vessel upon vessel of cells all having the same passage number were prepared, and then seeded with virus for the production of vaccine. That created an enormous logistical problem of managing preproduction batches and harvesting the virus at the optimum time. Key to that method was the production number of the cells: the production number had to be the

same for every production batch. As Applicant explains: "In classical serial production lines the number of doubling of the cells derived from the MWCS at the moment of harvest is known up front within certain limits. A maximum allowable generation number is set to the production system at the onset." Applicant' s specification at p. 4, lines 15-17.

Now, Applicant discloses methods that do not require strict adherence to production number. Indeed, "Production passage number (the number of cell passages used prior to production of the biological product), hence, is irrelevant within the limits set by ECB." Applicant's specification at p. 4, lines 20-21. Production number according to the present invention is "irrelevant" in the sense that the same production number is no longer required in all production batches. As Applicant explains, "Once such ECB is fully characterised one may allow to produce the product with cells at any passage number between MCB and ECB[.]" *Id.,* lines 29-31. Therefore, a *different* passage number can be used in production batches, and in some embodiments, the logistical problems mentioned above can be lessened.

Further, in classical serial production, as described in Griffiths and Wiktor, the number of doubling of cells derived from the manufacturers working cell bank at the moment of harvest is known up front within certain limits. *See* Applicant's specification at p. 4, lines 15-16. A maximum allowable generation number is set to the production system at the onset. *Id*. at lines 16-17. In contrast, in the claimed method, a bioreactor (manufacturer's working cell bank) is fed with cells from the master cell bank. The cells from the working cell bank are propagated to a specific and characterized passage number for an extended cell bank. *See id*. at lines 19-20. Once the extended cell bank

is fully characterized it allows one to produce the biological product with cells at any passage number between master cell bank and extended cell bank since it may be assumed that the cells have not changed. *See id.* at lines 29-32. As a result, tests on the manufacturer's working cell bank can be limited to sterility testing, which is a particular advantage of the claimed invention. *See id.* at lines 32-33.

Shimizu does not cure the deficiencies of Wiktor and Griffiths discussed above. Shimizu teaches using multiple fermentors for repeated batch cultivation for non-growth-associated products. However, there is nothing in Shimizu that teaches or suggests using such a process for anchorage dependent cells, *e.g.*, MDCK cells. Indeed, Shimizu does not even mention anchorage-dependent cells or MDCK cells. Thus, there is no reason why one of ordinary skill in the art would have combined the processes of Wiktor, Griffiths, and Shimizu with any reasonable expectation of success, and without the benefit of hindsight, which is impermissible. *See* M.P.E.P. § 2142.

For at least the foregoing reasons, the Examiner failed to establish a *prima facie* case of obviousness over Wiktor alone or in combination with Griffiths and Shimizu. Thus, Applicant respectfully requests that the Examiner reconsider and withdraw each of the foregoing rejections.

III. DOUBLE PATENTING REJECTION

Claims 45-76 are provisionally rejected for obviousness-type double patenting as allegedly unpatentable over co-pending Application No. 11/654,556. Final Office Action at p. 25.

While Applicant respectfully submits that the present invention is not obvious over any claim of the cited application, solely to expedite allowance of the present

application, Applicant presently plans to file a terminal disclaimer to overcome this rejection. However, because the rejection is based on a currently co-pending application, Applicant will wait to receive a Notice of Allowance in this or the co-pending case. At such time, Applicant will then review the claims in both applications to determine if the present plan is still appropriate.

IV. CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: 

Jennifer R. Gupta
Reg. No. 54,257